and randomized controlled trials of its effectiveness are underway.[1] Trials of clonidine have demonstrated a modest, statistically significant reduction in hot flashes, but the benefit was tempered by adverse effects (dry mouth, constipation, drowsiness and insomnia).[1]

***Prevention:*** Although less well studied, behavioural interventions may also decrease hot flashes. Relaxation techniques and exercise programs can mediate their severity. Daily doses of vitamin E (800 IU/d) improve symptoms slightly. Efforts to maintain a lower body core temperature by maintaining good air circulation, sipping cold drinks and lowering the thermostat can also help, as does avoiding alcohol, spicy foods and cigarettes.

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**References**

1. Shanafelt T, Barton D, Adjei A, Loprinzi C. Pathophysiology and treatment of hot flashes. *Mayo Clin Proc* 2002;77:1207-18.
2. Loprinzi CL, Michalak JC, Quella SK, O'Fallon JR, Hatfield AK, Nelimark RA, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347-52.
3. Taylor M. Alternatives to HRT: an evidence-based review. *Int J Fertil Womens Med* 2003;48(2):64-8.
4. Jacobson JS, Troxel AB, Evans J, Klaus L, Vahdat L, Kinne D, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol* 2001;19:2739-45.
5. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059-63.

**IN THE LITERATURE**

# Is there sustained renal benefit from previous intensive insulin therapy in people with type 1 diabetes?

Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type I diabetes mellitus on development and progression of diabetic nephropathy. *JAMA* 2003;290:2159-67.

***Background:*** The benefits of intensive insulin therapy for type 1 diabetes mellitus to prevent microvascular complications have been established.[1] However, it is unknown whether these benefits persist when insulin therapy becomes less intensive and begins to approximate that of conventional treatment.

***Design:*** In a randomized controlled trial, 1441 patients with type 1 diabetes were randomly assigned to receive either intensive insulin therapy to achieve normal glycosylated hemoglobin ($HbA_{1C}$) levels or conventional therapy (1 or 2 daily injections of insulin) without specific goals for glycemic control. Patients were eligible if they had no advanced diabetes complications and normal renal function. Following completion of the trial, a follow-up study of the cohort was begun in which patients who had been receiving the intensive therapy were encouraged to continue it and those in the conventional treatment arm were encouraged to switch to intensive treatment. Of the original 1441 subjects, 1375 agreed to participate in the follow-up study. No treatment intervention was involved, and participants were assessed for renal outcomes over 7–8 years.

***Results:*** After completion of the initial randomized controlled trial, patients in the intensive therapy arm had significantly lower $HbA_{1C}$ levels and a lower incidence of microalbuminuria than those receiving conventional treatment did (Table 1).

**Table 1: Outcome measures of previous intensive insulin therapy versus conventional therapy in patients with type 1 diabetes**

| Outcome | Intensive insulin therapy *n = 676* | Conventional therapy *n = 673* | *p* value |
|---|---|---|---|
| **At end of initial study** | | | |
| Mean $HbA_{1c}$ level, % | 7.4 | 9.1 | < 0.001 |
| Microalbuminuria, % of patients | 7.4 | 12.9 | < 0.001 |
| **At follow-up at 7–8 yr** | | | |
| Mean $HbA_{1c}$ level, % | 8.0 | 8.2 | 0.002 |
| New microalbuminuria, % of patients | 6.8 | 15.8 | < 0.001 |
| New clinical albuminuria, % of patients | 1.4 | 9.4 | < 0.001 |
| Hypertension, % of patients | 29.9 | 40.3 | < 0.001 |
| Creatinine > 177 mmol/L, no. of patients | 5 | 19 | < 0.004 |

Note: HbA1c = glycosylated hemoglobin.

The glomerular filtration rate and creatinine clearance were identical in both groups.

The difference in $HbA_{1C}$ levels between the 2 groups began to narrow during the follow-up study, although the modest difference remained statistically significant. More impressive was that the patients in the intensive treatment arm had significantly lower incidences of microalbuminuria, clinical albuminuria, hypertension and creatinine levels of more than 177 mmol/L (Table 1).

***Commentary:*** The results of this study suggest that the benefits of strict glycemic control on renal function are long-lasting. A similar observation has been made regarding diabetic retinopathy.[2] These results lend support to the hypothesis that diabetic complications are invoked by a "metabolic memory" effect (one or more processes set in motion by previous periods of poor metabolic or glucose control and that culminate in tissue damage). One example is the formation of advanced glycation end products, which can have extremely long half-lives.[3] Alternatively, it is possible that excellent glycemic control merely delays the development of diabetic complications.

That the investigators used the surrogate end point of albuminuria rather than a clinical end point is not a crucial concern, because albuminuria is known to be strongly predictive of end-stage renal disease.[4] Also, although the difference in mean $HbA_{1C}$ levels between the 2 groups was statistically significant over the course of the study, it was very small and unlikely to account for the results. Finally, because the study population had been carefully screened to capture individuals with high motivation, it is not representative of the entire population with type 1 diabetes.

***Practice implications:*** Provided there are no contraindications to intensive therapy (poor compliance, advanced diabetic complications or hypoglycemic unawareness) all patients with type 1 diabetes should be considered for intensive insulin therapy. Physicians and diabetic patients should be gratified to learn from this study that, even if a patient's intensive therapy must be abandoned one day, it will likely continue to confer benefits long afterward.

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## References

1. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
2. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type I diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381-9.
3. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813-20.
4. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease: with emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 1983;32(Suppl 2):64-78.